SEDATIVE AND HYPNOTIC

DR. MADHURI PANDOLE
ASSISTANT PROFESSOR
SARASWATI INSTITUTE OF PHARMACEUTICAL SCIENCES
DHANAP , GANDHINAGAR

SEDATIVE

- These are the drugs that decrease activity and excitement of the patient and calm the anxiety by producing mild depression of CNS without causing drowsiness or sleep.

HYPONTIC

- These are the drugs that produce drowsiness, compelling the patient to sleep by depressing the CNS, particularly the reticular activatinf factor(RAF) which characterized wakefulness.

NORMAL SLEEP

Normal sleep cyclic and repetitive, consists of distinct stages, based on three physiologic measures:the electroencephalogram, the electromyogram, and the electrostagmogram.

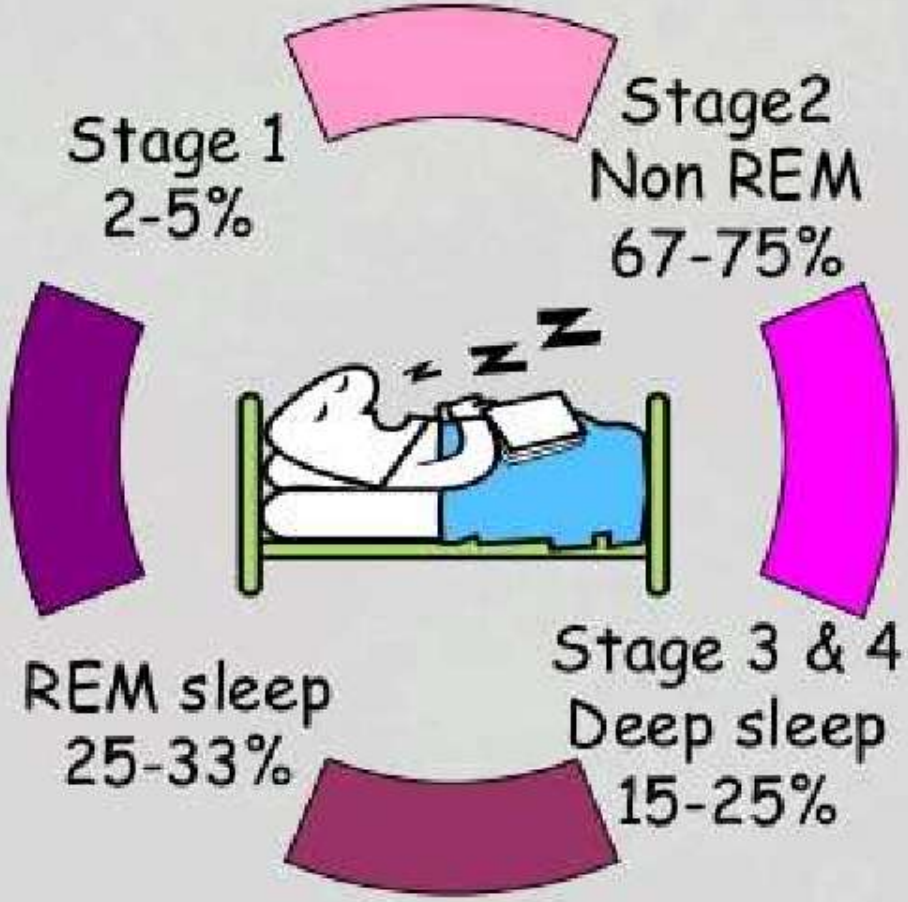
- Rapid eye moment(REM)sleep
- Non-rapid eye moment(NREM)sleep:

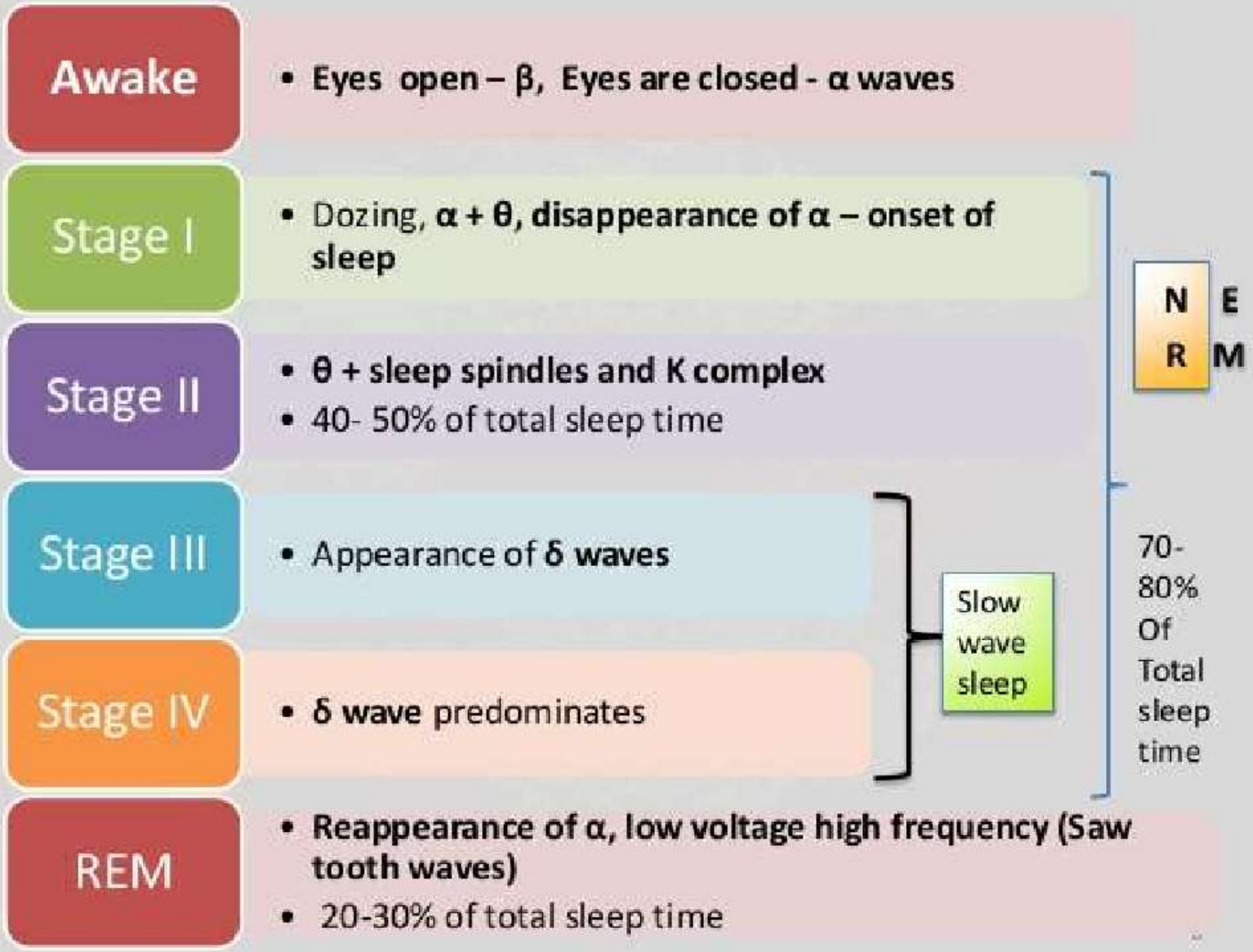
  70%-75%

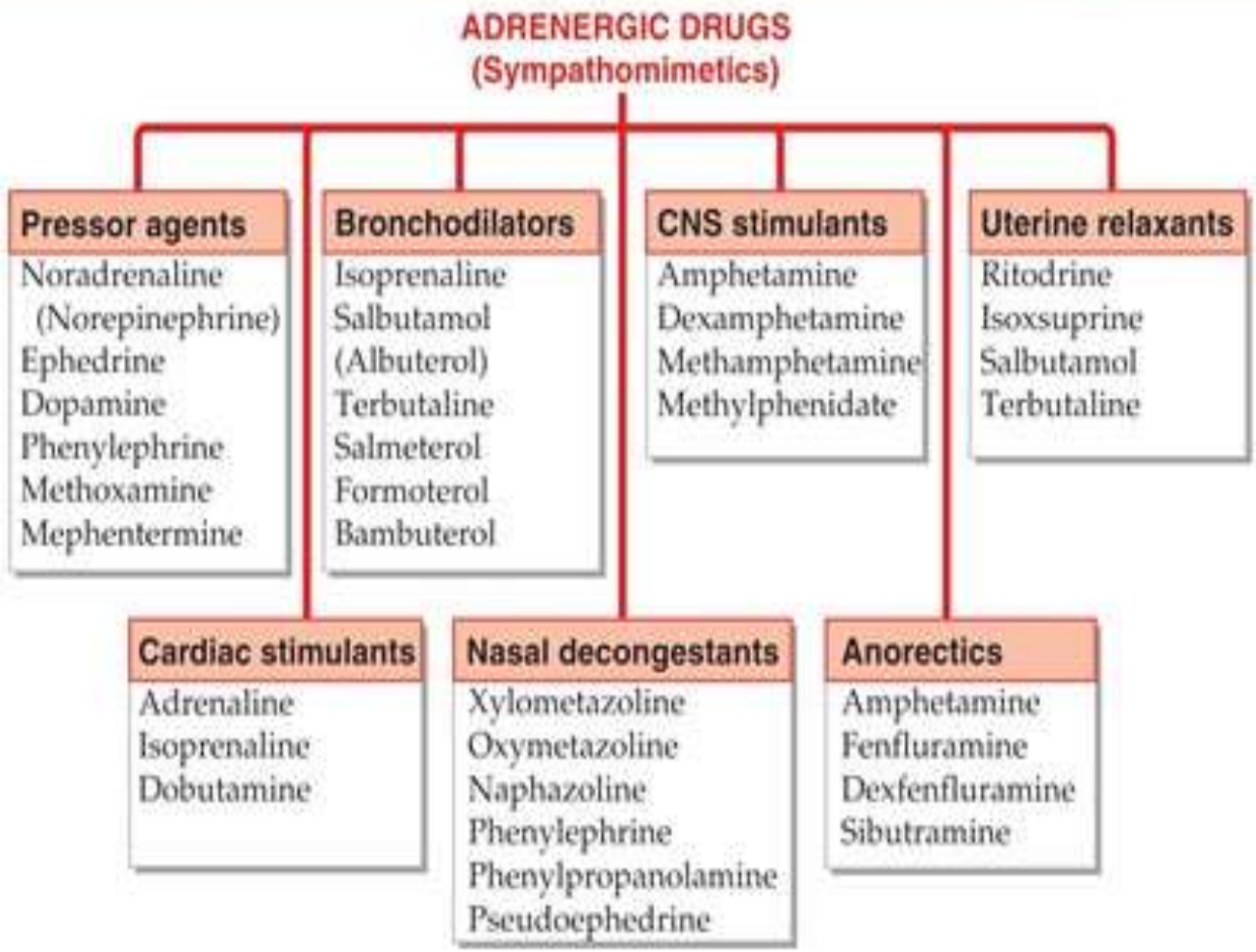
  Stage 1,2

  Stage 3,4:slow wave sleep, SWS

Stages of Sleep




Awake
• Eyes open – β, Eyes are closed - α waves
Stage I
• Dozing, α + θ, disappearance of α – onset of sleep
Stage II
• θ + sleep spindles and K complex
• 40- 50% of total sleep time
Stage III
• Appearance of δ waves
Stage IV
• δ wave predominates
Slow wave sleep
N R E M
70-80% Of Total sleep time
REM
• Reappearance of α, low voltage high frequency (Saw tooth waves)
• 20-30% of total sleep time

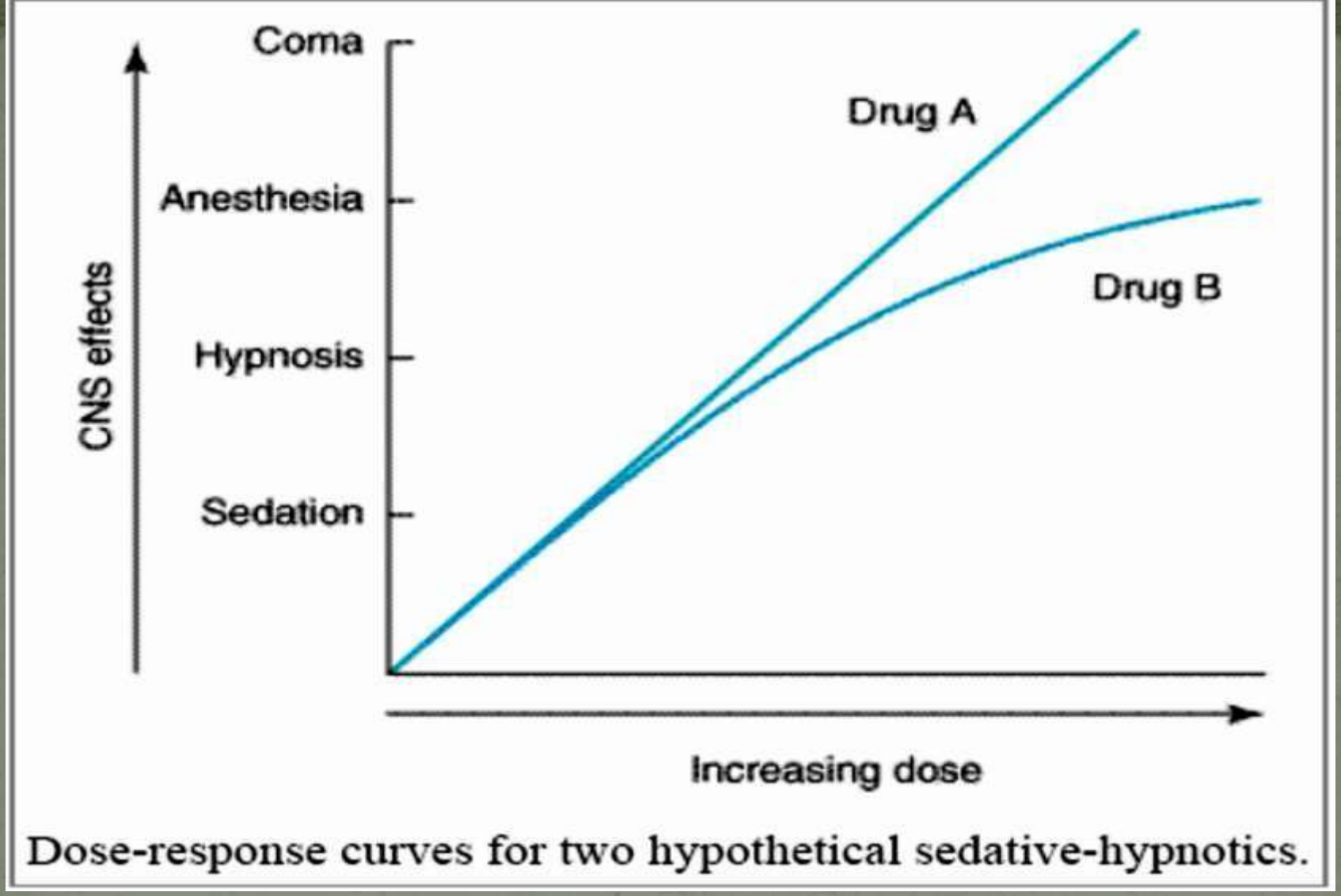

ADRENERGIC DRUGS
(Sympathomimetics)
Pressor agents
Noradrenaline
(Norepinephrine)
Ephedrine
Dopamine
Phenylephrine
Methoxamine
Mephentermine
Bronchodilators
Isoprenaline
Salbutamol
(Albuterol)
Terbutaline
Salmeterol
Formoterol
Bambuterol
CNS stimulants
Amphetamine
Dexamphetamine
Methamphetamine
Methylphenidate
Uterine relaxants
Ritodrine
Isoxsuprine
Salbutamol
Terbutaline
Cardiac stimulants
Adrenaline
Isoprenaline
Dobutamine
Nasal decongestants
Xylometazoline
Oxymetazoline
Naphazoline
Phenylephrine
Phenylpropanolamine
Pseudoephedrine
Anorectics
Amphetamine
Fenfluramine
Dexfenfluramine
Sibutramine

Barbiturates

- enhance the binding of GABA to $GABA_A$ receptors
- Prolonging duration
- Only α and β (not ϒ) subunits are required for barbiturate action
- Narrow therapeutic index
- in small doses, barbiturates increase reactions to painful stimuli.
- Hence, they cannot be relied on to produce sedation or sleep in the presence of even moderate pain.

Bezodiazepines

- enhance the binding of GABA to $GABA_A$ receptors
- increasing the frequency
- Unlike barbiturates, benzodiazepines do not activate $GABA_A$ receptors directly



Dose-response curves for two hypothetical sedative-hypnotics.

Graded dose-dependent depressive effect of sedative- hypnotics on central nervous system function

BENZODIAZEPINES

Mechanism of Action-

- BDZs potentiate GABAergic inhibition at all levels of the neuraxis.
- BDZs cause more frequent openings of the GABA-Cl^- channel via membrane hyperpolarization, and increased receptor affinity for GABA.
- BDZs act on BZ_1 (α_1 and α_2 subunit-containing) and BZ_2 (α_5 subunit-containing)receptors.
- May cause euphoria, impaired judgement, loss of cell control and anterograde amnesic effects.

Effects- Dose-dependent depressant effects on the CNS including

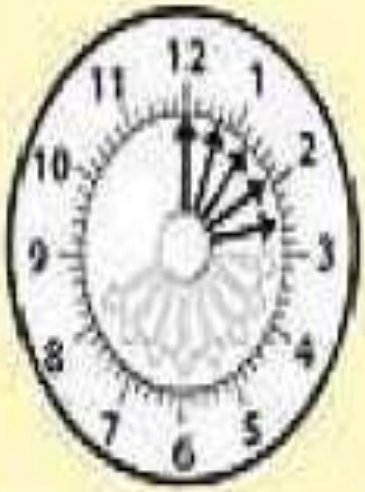
- Sedation
- Relief of anxiety
- Amnesia
- Hypnosis
- Anaesthesia
- Coma
- Respiratory depression steeperdose-response relationship than benzodiazepines

BARBITURATES CLASSIFIED ACCORDING TO THEIR DURATIONS OF ACTION

Long-acting

Phenobarbital

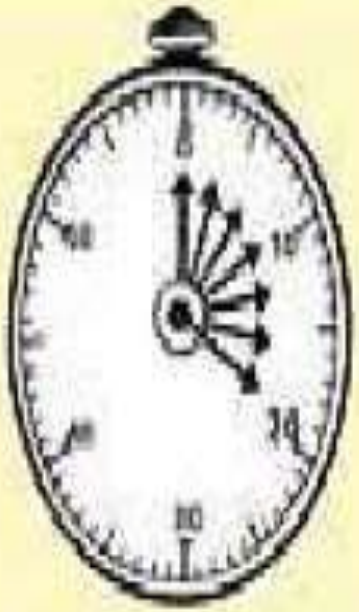
Short-acting



3-8 Hours

Pentobarbital
Secobarbital
Amobarbital

Ultra-short-acting



20 Minutes

Thiopental

ACTIONS

1. Depression of CNS: At low doses, the barbiturates produce sedation (calmingeffect, reducing excitement).

2. **Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdosage is** followed by respiratorydepression and death.
3. **Enzyme induction: Barbiturates induce P450 microsomal enzymes in the liver.**

PHARMACOKINETICS

- All barbiturates redistribute in the body.
- Barbiturates are metabolized in the liver, and inactive metabolites are excreted in the urine.
- They readily cross the placenta and can depress the fetus.
- **Toxicity:** Extensions of CNS depressant effects dependence liability > benzodiazepines.
- **Interactions:** Additive CNS depression with ethanol and many other drugs induction of hepatic drug-metabolizing enzymes.

ANESTHESIA (THIOPENTAL, METHOHEXITAL)

THERAPEUTIC USES

- Selection of a barbiturate is strongly influenced by the desired
  - duration of action.

- The ultrashort-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia.

- **ANXIETY**
- **Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia.**
  - When used as hypnotics, they suppress REM sleep more than other stages. However, most have been replaced by the benzodiazepines

ANTICONVULSANT: (PHENOBARBITAL, MEPHOBARBITAL)

- **Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia.**
- Phenobarbital has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures.
- However, phenobarbital can depress cognitive performance in children, and the drug should be used cautiously.
- Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression.

ADVERSE EFFECTS

1. **CNS:** Barbiturates cause **drowsiness**, **impaired concentration.**

2. **Drug hangover: Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes.**

3. **Barbiturates induce the P450 system.**

4. By inducing aminolevulinic acid (ALA) synthetase, barbiturates increase **porphyrin synthesis**, and are contraindicated in patients with acute intermittent porphyria.

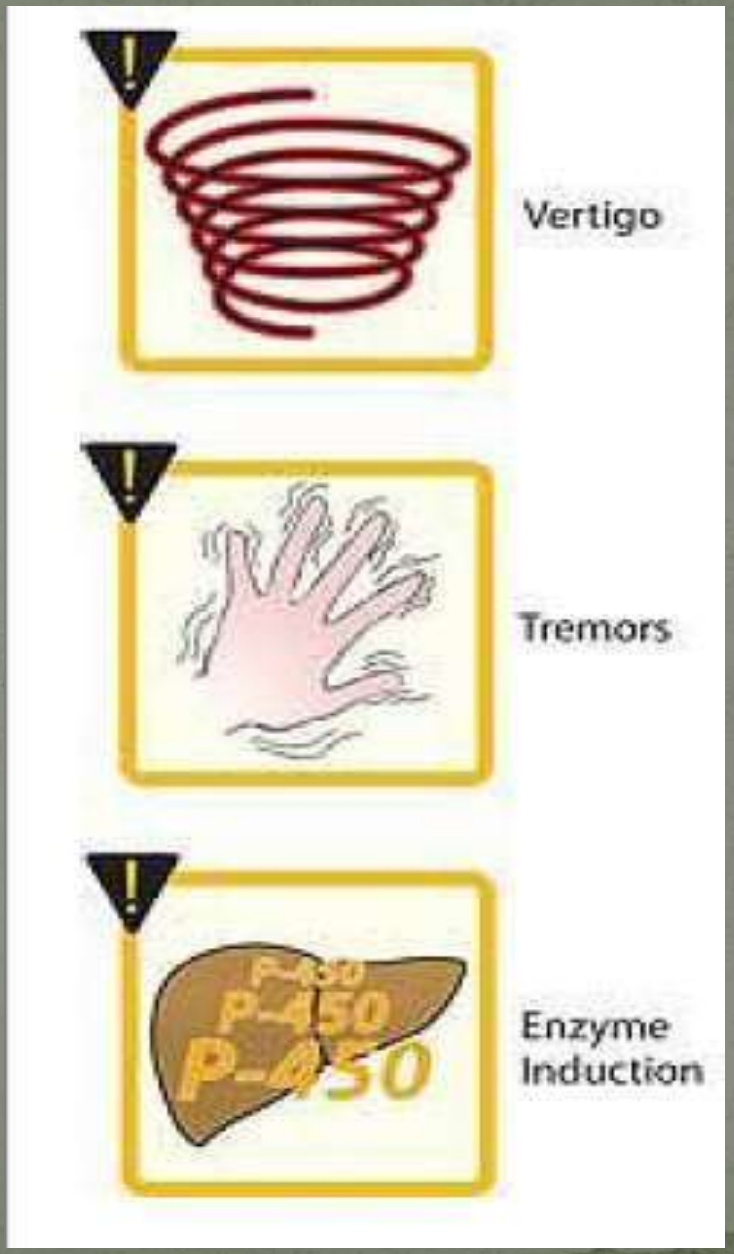
5. Physical dependence: Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest.

6. **Poisoning: Barbiturate poisoning has been a leading cause of death resulting from drug overdoses for many decades.**

   It may be due toautomatism.

- Severe depression of respiration is coupled with central cardiovascular depression, and results in a shock-like condition with shallow, infrequent breathing.


Potential for Addiction
Drowsiness
Nausea


Vertigo
Tremors
P-450
P-450
P-450
Enzyme Induction

THE TREATMENT OF ACUTE BARBITURATE INTOXICATION

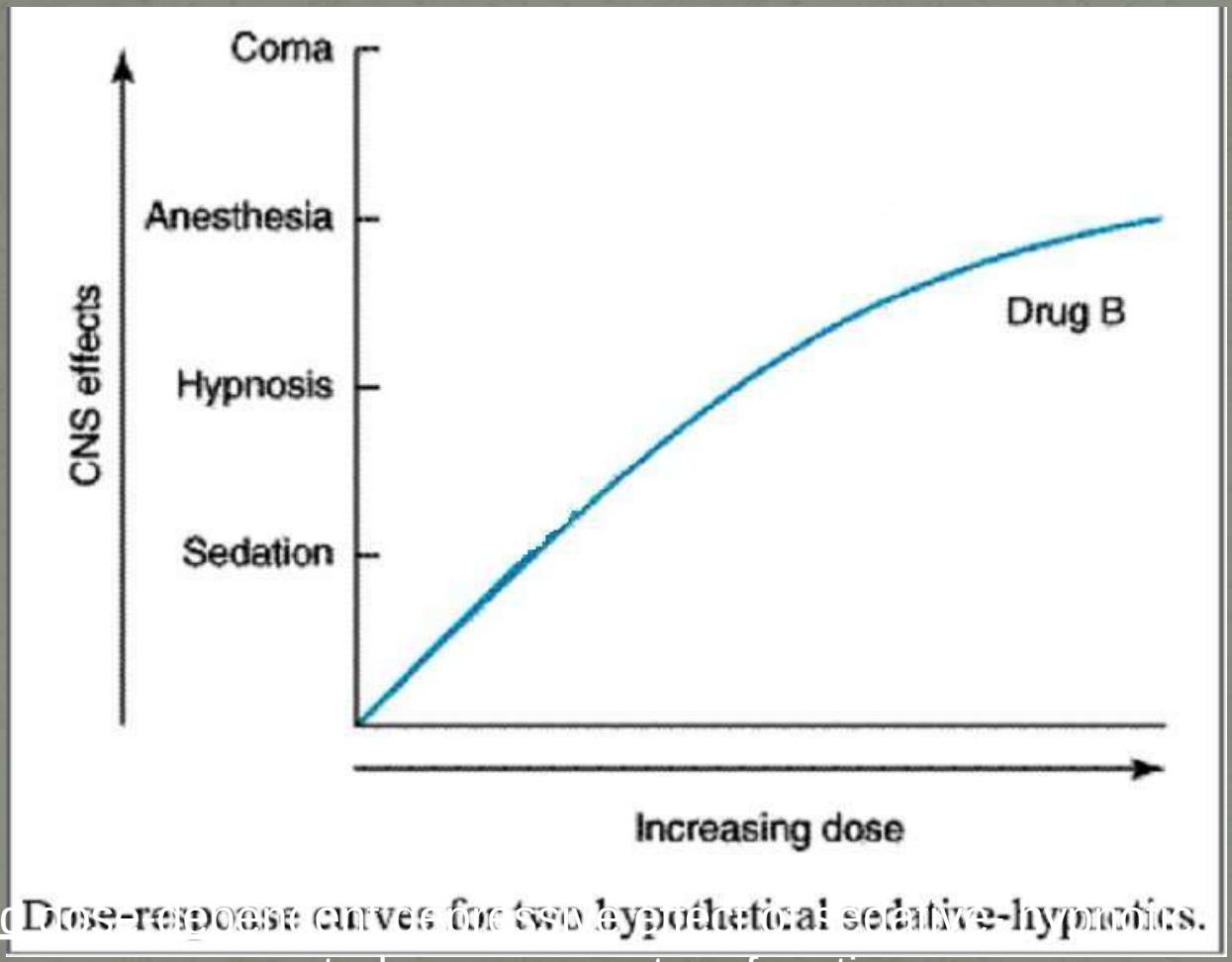
Treatment includes artificial respiration and purging the stomach of its contents if thedrug has been recently taken.

- **No specific barbiturate antagonist isavailable**.
- General supportive measures.
- Hemodialysis or hemoperfusion is necessary only rarely.
- Use of CNS stimulants is contraindicated becausethey increase the mortality rate.

THE TREATMENT OF ACUTE BARBITURATE INTOXICATION

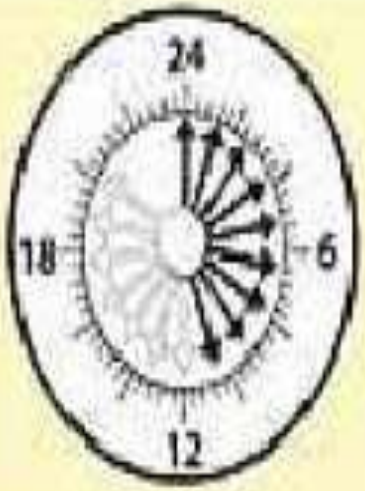
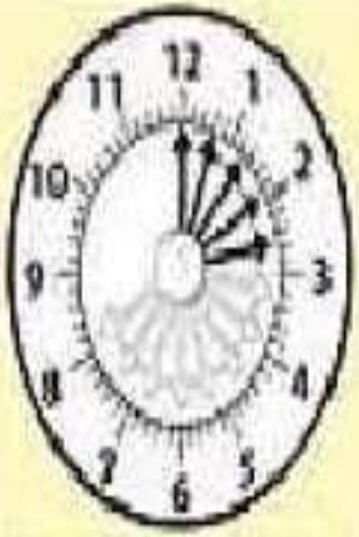
- If renal and cardiac functions are satisfactory, and the patient is hydrated, **forced diuresis and alkalinization** of the urine will hasten the excretionof phenobarbital.
- In the event of renal failure - hemodialysis
- circulatory collapse is a major threat. So hypovolemia must be corrected & blood pressure can be supported with dopamine.
- Acute renal failure consequent to shock and hypoxia accounts for perhaps one-sixth of the deaths.

BENZODIAZEPINES



Graded Dose-response curves for two hypothetical sedative-hypnotics. on central nervous system function

COMPARISON OF THE DURATIONS OF ACTION OF THE BENZODIAZEPINES

Long-acting	Intermediate-acting	Short-acting
	 10–20 Hours	 3–8 Hours
Clorazepate *Chlordiazepoxide* *Diazepam* *Flurazepam* *Quazepam*	*Alprazolam* *Estazolam* *Lorazepam* *Temazepam*	*Oxazepam* *Triazolam*

Effects of benzodiazepine

- On increasing the dose sedationprogresses to hypnosis and then tostupor.

- But the drugs do not cause a true general anesthesia because

  -awareness usually persists

  -immobility sufficient to allow surgery cannot be achieved.

- However at "preanesthetic" doses, there isamnesia.

Effects on the (EEG) and Sleep Stages

- ↓ sleep latency
- ↓ number of awakenings
- ↓ time spent in stage 0, 1, 3, 4
- ↓ time spent in REM sleep (↑number of cycles of REM sleep)
- ↑ total sleep time (largely by increasing the time spent in stage 2)

- Respiration-Hypnotic doses of benzodiazepines are without effect on respiration in normal subjects

- CVS-In preanesthetic doses, all benzodiazepines decrease blood pressure and increase heartrate

PHARMACOKINETICS

- A short elimination $t_{1/2}$ is desirable for hypnotics, although this carries the drawback of increased abuse liability and severity of withdrawal after drug discontinuation.
- Most of the BZDs are metabolized in the liver to produce active products (thus long duration of action).
- After metabolism these are conjugated and are excreted via kidney.

ADVERSE EFFECTS

- Light-headedness
- Fatigue
- **Increased reaction time**
- **Motor incoordination**
- Impairment of mental and motor functions
- **Confusion**
- Antero-grade **amnesia**
- Cognition appears to be affected less than motor performance.
- All of these effects can greatly impair driving and other psychomotor skills, especially if combined with ethanol.

FLUMAZENIL: A BENZODIAZEPINE RECEPTOR ANTAGONIST

- competitively antagonism
- Flumazenil antagonizes both the electrophysiological and behavioral effects of agonist and inverse-agonist benzodiazepines and β-carbolines.
- Flumazenil is available only for intravenous administration.
- On intravenous administration, flumazenil is eliminated almost entirely by hepatic metabolism to inactiveproducts with a **$t_{1/2}$ of ~1 hour**; the duration of clinical effects usually is only **30-60 minutes**.

FLUMAZENIL: A BENZODIAZEPINE RECEPTOR ANTAGONIST

PRIMARY INDICATIONS FOR THE USE OF FLUMAZENIL ARE:-

- Management of suspected benzodiazepine overdose.
- Reversal of sedative effects produced by benzodiazepines administered during either general anesthesia.

The administration of a series of small injections is preferred to a single bolus injection.

- A total of **1 mg** flumazenil given over 1-3 minutes usually is sufficient to abolish the effects of therapeutic doses of benzodiazepines.
- Patients with suspected benzodiazepine overdose should respond adequately to a cumulative dose of 1-5 mg given over 2-10 minutes;
- A lack of response to 5 mg flumazenil strongly suggests that a benzodiazepine is not the major cause of sedation.

Novel Benzodiazepine Receptor Agonists

- **Z compounds**
  zolpidem , zaleplon , zopiclone and **eszopiclone**

- structurally unrelated to each other and to benzodiazepines

- therapeutic efficacy as hypnotics is due to agonist effects on the benzodiazepine site of the $GABA_A$ receptor

- Compared to benzodiazepines, **Z compounds** are
  -less effective as anticonvulsants or muscle relaxants
  -which may be related to their relative selectivity for $GABA_A$ receptors containing the **α1** subunit.

Novel Benzodiazepine Receptor Agonists

- The clinical presentation of overdose with **Z compounds** is similar to that of benzodiazepine overdose and can be treated with the benzodiazepine antagonist flumazenil.

- Zaleplon and zolpidem are **effective in relieving sleep-onset insomnia**. Both drugs have been approved by the FDA for use for up to **7-10 days** at a time.

- Zaleplon and zolpidem **have sustained hypnotic efficacy** without occurrence of rebound insomnia on abrupt discontinuation.

ZALEPLON

- Its plasma $t_{1/2}$ is ~1 hours

- approved for use immediately at bedtime or when the patient has difficulty falling asleep after bedtime.

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BUSPIRONE

- Most selective anxiolytic currently available.
- The anxiolytic effect of this drug takes several weeks to develop => used for GAD.
- Buspirone does not have sedative effects and does not potentiate CNS depressants.
- Has a relatively high margin of safety, few side effects and does not appear to be associated with drug dependence.
- No rebound anxiety or signs of withdrawal when discontinued.

Mechanism of Action:

- Acts as a partial agonist at the 5-HT_{1A} receptor presynaptically inhibiting serotonin release.
- The metabolite 1-PP has α_2 -AR blocking action.

Side effects:

- Tachycardia, palpitations, nervousness, GI distress and paresthesias may occur.
- Causes a dose-dependent pupillary constriction.

Pharmacokinetics of BUSPIRONE

- Not effective in panic disorders.
- Rapidly absorbed orally.
- Undergoes extensive hepatic metabolism (hydroxylation and dealkylation) to form several active metabolites (e.g. 1-(2-pyrimidyl-piperazine, 1-PP)
- Well tolerated by elderly, but may have slow clearance.
- Analogs: Ipsapirone, gepirone, tandospirone

Zolpidem

- Structurally unrelated but as effective as BDZs.
- Minimal muscle relaxing and anticonvulsant effect.
- Rapidly metabolized by liver enzymes into inactive metabolites.
- Dosage should be reduced in patients with hepatic dysfunction, the elderly and patients taking cimetidine.

Mechanism of Action:

- Binds selectively to BZ_1 receptors.
- Facilitates GABA-mediated neuronal inhibition.

- Actions are antagonized by flumazenil

Chloral hydrate

- Is used in institutionalized patients. It displaces warfarin (anti-coagulant) from plasma proteins.
- Extensive biotransformation.

α2-Adrenoreceptor Agonists (eg. Clonidine)

- Antihypertensive.
- Has been used for the treatment of panic attacks.
- Has been useful in suppressing anxiety during the management of withdrawal from nicotine and opioid analgesics.
- Withdrawal from clonidine, after protracted use, may lead to a life-threatening hypertensive crisis.

β-Adrenoreceptor Antagonists (eg. Propranolol)

- Use to treat some forms of anxiety, particularly when physical (autonomic) symptoms (sweating, tremor, tachycardia) are severe.
- Adverse effects of propranolol may include: lethargy, vivid dreams, hallucinations.

Prescribing Guidelines for the Management of Insomnia

Hypnotics that act at **$GABA_A$** receptors, including the benzodiazepine hypnotics and the newer agents zolpidem, zopiclone, and zaleplon, are preferred to barbiturates because they have a

- **Greater therapeutic index**
- **Less toxic in overdose**
- **Have smaller effects on sleep architecture**
- **Less abuse potential**.

Compounds with a **shorter $t_{1/2}$** are favored in patients with sleep-onset insomnia but without significant daytime anxiety who need to function at full effectiveness during the day.

- These compounds also appropriate for the elderly because of a decreased risk of falls and respiratory depression.
- One should be aware that early-morning awakening, rebound daytime anxiety, and amnestic episodes also may occur.
- These undesirable side effects are more common at higher doses of the benzodiazepines.

Prescribing Guidelines for the Management of Insomnia

- **Benzodiazepines with longer $t_{1/2}$**

  are favored for patients

  - --- who have significant daytime anxiety and

  ----- who may be able to tolerate next-day sedation.

- However can be associated with

  -next-day cognitive impairment

  -delayed daytime cognitive impairment (after 2-4 weeksof treatment) as a result of drug accumulation with repeated administration.

Older agents such as barbiturates, chloral hydrate, and meprobamate have high abuse potential and are dangerous in overdose.

Management of Patients after Long-Term Treatment with Hypnotic Agents

- If a benzodiazepine has been used regularly for **>2 weeks**, it should be tapered rather than discontinued abruptly.
- In some patients on hypnotics with a short $t_{1/2}$, it is easier to switch first to a hypnotic with a long $t_{1/2}$ and then to taper.
- The onset of withdrawal symptoms from medications with a long $t_{1/2}$ may bedelayed.
- Consequently, the patient should be warned about the symptoms associated with withdrawal effects.

THANK YOU